PATENT

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of: John C. Hiserodt	Art Unit: 1633
Serial No.: 09/162,648	Examiner: Carrie M. Stroup, Ph.D.
Filing Date: September 29, 1998	
For: CANCER IMMUNOTHERAPY USING ALLOSTIMULATED CELLS IN A MULTIPLE SEQUENTIAL IMPLANTATION STRATEGY	

DECLARATION BY TETSUYA GATANAGA

PURSUANT TO 37 C.F.R. § 1.56

REGARDING CLINICAL TRIAL CONDUCTED UNDER IND-6288

The Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Dear Sir:

I, TETSUYA GATANAGA, Ph.D., do hereby declare as follows:

1. I am Vice President for Research and Development at Meyer Pharmaceuticals™ LLC. I have extensive research experience in the fields of cellular and molecular biology and immunology. A copy of my curriculum vitae is attached to this Declaration as Appendix A.

2. Meyer Pharmaceuticals™ is a privately held biotechnology company located at 1761 Kaiser Avenue, Irvine, California 92614. The Company owns the technology described in this patent application, and holds an exclusive license to the technology described in issued U.S. Patent 5,837,233. As part of my responsibility, I have been overseeing the production of Cytoimplant™, alloactivated lymphocytes for implantation into human cancer patients according to the invention claimed in this application.

3. In a previously completed PhaseI/II clinical study conducted under IND-6288, Cytoimplant™ cells were administered at a single trumor site to ten patients with pancreatic cancer, nine of whom had locally advanced Stage II, III, or IV tumors, and one of whom had a Stage I tumor. The study was designed to examine the feasibility, tolerability and toxicity associated with three dose levels of Cytoimplant™ cells (3, 6, and 9×10^9 cells). Patient survival was measured from the time of treatment to the time of death. Tumor response was measured by serial CT scans or endoscopic ultrasound.

Results were as follows: Karnofsky Performance scores remained stable or increased in 9 of 10 patients over the follow-up period. With respect to the safety profile, elevated bilirubin, liver enzymes and nausea/vomiting with dehydration were the most common adverse effects documented, and were attributed to obstruction of biliary stents by the underlying disease, rather than a consequence of treatment.

The median survival for all patients was 11.5 months (range 4.2 to >21 months). The 6–month, 9-month, and 12-month probability of survival was 80% (n=8), 60% (n=6), and 50% (n=5), respectively. Documented tumor responses evaluated at 3 and 6 months were as follows: 2 partial responses, 1 minor response, 3 stable disease, and 4 with progressive disease.

4. In the fall of 1998, Meyer Pharmaceuticals™ sponsored a multicenter open randomized clinical trial to compare the effect of Cytoimplant™ with gemcitabine (Gemzar®) on late stage unresectable pancreatic cancer. I oversaw the production of each Cytoimplant™ by our manufacturing facility, and participated in the design and execution of the trial with the Chief Medical Officer, Dr. Jan Drayer.

5. Gemcitabine is to my knowledge the best currently approved drug for treatment of advanced pancreatic cancer. In an IND treatment program reported by Storniolo et al. (Cancer 85:1261, 1999), over 3000 patients were enrolled and treated with cycles of gemcitabine as follows: 1000 mg/m^2 weekly × 7 weeks, 1 week rest, then cycles of 3 weeks treatment and 1 week rest thereafter. Disease related symptom improvement (DRSI) was measured as improvement in pain, analgesic class, or Karnofsky performance scale, or improved stability in any of these parameters. 18.4% of the pateints had improved DSRI after 4 cycles. For the 982 patients with tumor response data, 10.6% showed a parital response, and 1.4% showed a complete response. A copy of the Sorniolo article, and other publications on gemcitabine, are being filed in this application in conjunction with this Declaration.

6. The recent trial sponsored by Meyer Pharmaceuticals™ was conducted under Protocol No. AIT-PAN-201, approved by the U.S. Food and Drug Administration under BB-IND-6288. Patients entered into the trial had unresectable adenocarcinoma of the pancreas, a Karnofsky performance score of at least 70, minimum laboratory parameters, and had given informed consent for the treatment. They were assigned randomly to the Cytoimplant™ arm or the gemcitabine arm of the trial, at a 2:1 ratio.

Patients in the gemcitabine group were given intravenous chemotherapy on an out-patient basis, at a dose of 1000 mg/m^2 weekly for up to 7 weeks, and then cycled in a fashion similar to that outlined in Storniolo et al.

Patients in the Cytoimplant™ group were given two intratumor implants. The alloactivated lymphocytes were prepared in our facility by combining alloactivating peripheral blood mononuclear cells (PBMC) of volunteer unrelated donors with irradiated patient PBMC, and culturing for 3 days in a closed system. The Cytoimplant™ was administered to each patient using an endoscopic ultrasound guided injection technique, in which an echoendoscope was used to position a 19 or 22 gauge needle in the primary tumor mass. The Cytoimplant™ cells (~9×10^9 mononuclear cells in ~ 9 mL) were injected over a 2-5 min period. When possible, a second Cytoimplant™ was given 4-5 months later.

The first patient (01-001) was entered into the program on December 10, 1998. The last two patients (05-208 and 07-308) were entered into the program on October 18, 1999.

7. Follow-up was conducted bimonthly, and included blood work, an abdominal CT scan, and a subject questionnaire. Before the trial commenced, the primary efficacy endpoint was defined as a relative improvement in overall patient survival, based on a proportional hazards model, stratifying for the stage of the disease. Secondary efficacy endpoints were objective tumor response, progression-free survival, time to treatment failure, and quality of life. The study also had the objective to compare the safety of Cytoimplant™ with gemcitabine in this patient population.

Data accumulated up to November 10, 1999 has now been compiled, and is attached to this Declaration as Appendix B.

8. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

3/2/00
3/2/00

Date

Tetsuya Gatanaga, Ph.D.